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Evaluation of paliperidone palmitate long-acting injectable antipsychotic therapy as an early treatment option in patients with schizophrenia

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Abstract

Aim: This exploratory post hoc analysis of a randomized, double-blind (DB), multicentre, non-inferiority study (NCT01515423) evaluated the effects of the long-acting injectable antipsychotic therapies once-monthly paliperidone palmitate (PP1M) and once-every-3-months paliperidone palmitate (PP3M) on symptom severity and functional remission in patients with schizophrenia with differing durations of illness (≤5, 6-10 and >10 years).

Methods: Endpoints included Personal and Social Performance (PSP) scale and Positive and Negative Syndrome Scale (PANSS) total scores during the DB phase (DB baseline and DB endpoint) and the proportion of patients meeting PSP or PANSS remission criteria at any time during the open-label (OL) or DB phases that were maintained for ≥3, ≥6, ≥9 or ≥12 months.

Results: In both the OL and DB phases, significant improvements in PSP scale and PANSS scores were observed from baseline in all duration-of-illness groups, with significantly greater improvements observed in the ≤5-year and 6-10-year groups compared with the >10-year group. The proportion of patients who maintained PSP or PANSS remission criteria for ≥3, ≥6, ≥9 and ≥12 months was higher in the ≤5-year and 6-10-year groups than in the >10-year group. Safety profiles were similar across duration-of-illness groups in the DB phase.

Conclusions: Symptomatic and functional improvements were observed with PP1M/PP3M in patients with differing durations of schizophrenia, but the magnitude of the effects was greater in those with early illness vs chronic illness. These findings advocate implementation of PP1M and PP3M in all stages of schizophrenia, including early illness.

KEYWORDS
antipsychotic medication, early illness, long-acting injectable, paliperidone palmitate, schizophrenia

1 | INTRODUCTION

In persons with schizophrenia, the greatest deterioration in symptoms occurs during the first 5 years after diagnosis (Lieberman et al., 2001), and studies show that treatment responses decrease with each psychotic episode (McGlashan & Johannessen, 1996). Therefore, the early and sustained management of symptoms is warranted to impede symptomatic and functional deterioration. However, persons recently diagnosed with schizophrenia and those experiencing first-episode psychosis are most vulnerable to inadequate treatment because of non-adherence (Perkins et al., 2008). This vulnerability has been attributed to young age, inaccurate perception of the benefits of treatment and poor disease insight (Coldham, Addington, & Addington, 2002; Perkins et al., 2006).

Some evidence suggests that early intervention improves clinical and overall outcomes for patients (Alonso et al., 2009; Alphs, Bossie, Mao, Lee, & Starr, 2015; Canuso et al., 2010; Mihalopoulos, Harris, Henry, Harrigan, & McGorry, 2009; Subotnik et al., 2015). Results have been conflicting with respect to the value of long-acting injectables (LAIs) over oral antipsychotics (Fusar-Poli, 2013; Kishimoto et al., 2014). However, LAI antipsychotics may combat adherence issues (Bosanac & Castle, 2016; Brissos, Veguilla, Taylor, & Balanza-Martinez, 2014), make adherence transparent and improve prescriber knowledge of non-adherence, lower relapse rates, delay functional deterioration and improve overall outcomes for patients and caregivers (Bosanac & Castle, 2016; Brissos et al., 2014). Despite these potential advantages, the use of LAIs has been recommended historically only after recurrent relapses related to partial or complete non-adherence or in response to patient preference of the LAI formulation (Lehman, 2004). Canadian treatment guidelines, however, acknowledge increasing evidence to support the use of LAIs earlier in the course of treatment (Remington et al., 2017).

Although several studies have shown the potential benefits of LAIs in patients with early-illness schizophrenia (Bartzokis et al., 2012; Nuechterlein, Ventura, Subotnik, & Bartzokis, 2014; Schreiner et al., 2015; Sliwa, Bossie, Fu, Turkoz, & Alphs, 2012; Subotnik et al., 2015; Weiden et al., 2009), the effectiveness of once-monthly paliperidone palmitate (PP1M) and once-every-3-months paliperidone palmitate (PP3M) LAIs on early illness has not been investigated. The objective of this exploratory post hoc analysis of a randomized, double-blind (DB), multicentre, non-inferiority trial (NCT01515423) was to evaluate the effect of PP1M and PP3M on symptom severity and functioning in patients with schizophrenia with differing durations of illness.

2 | MATERIALS AND METHODS

The original study was reviewed appropriately by an independent ethics committee or institutional review board, in compliance with the Declaration of Helsinki and consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written informed consent before enrolment. The methodology has been described previously (Savitz et al., 2016) and is described briefly here.

2.1 | Study design

This exploratory post hoc analysis of a randomized, DB, parallel-group, multicentre, non-inferiority study (NCT01515423) was conducted April 2012-March 2015 at 199 sites in 26 countries. The study consisted of three phases: a screening/washout/tolerability phase (≤3 weeks), an open-label (OL) stabilization phase (17 weeks, flexible doses) and a DB phase (48 weeks, fixed doses). During the OL phase, patients received PP1M for 17 weeks per the following dosing schedule: day 1: 234 mg (deltoid); day 8: 156 mg (deltoid); weeks 5 and 9: flexibly dosed (78, 117, 156 or 234 mg deltoid or gluteal); and week 13: same dose of PP1M as at week 9. To enter the DB phase, patients had to meet stabilization criteria at the end of the OL phase, defined as Positive and Negative Syndrome Scale (PANSS) total score <70; score of ≤4 for PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behaviour), P6 suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness) and G14 (poor impulse control); and reduction in Clinical Global Impressions-Severity scale score ≥1. During the DB phase, patients were randomly assigned 1:1 to PP1M (78, 117, 156 or 234 mg) or PP3M (274, 410, 546 or 819 mg) in fixed doses that matched the doses selected at the end of the OL phase.

2.2 | Inclusion/exclusion criteria

Inclusion criteria for enrolment were individuals aged 18-70 years with a *DSM-IV* diagnosis of schizophrenia for ≥1 year before screening, total PANSS scored 70-120 at screening and baseline and worsening of symptoms.

2.3 | Assessments and endpoints

A patient's severity of schizophrenia symptoms was assessed using the 30-item PANSS (Kay, Fiszbein, & Opler, 1987), and patient functioning was assessed using the Personal and Social Performance (PSP) scale (Nasrallah, Morosini, & Gagnon, 2008). The PANSS was administered at screening, baseline, weeks 1, 5, 9, 13 and 14 of the OL phase, and every 4 weeks during the DB phase beginning at week 17. The PSP was administered at baseline, at week 9 of the OL phase, and every 12 weeks during the DB phase beginning at week 17. Since PP1M and PP3M were the same molecule with different delivery systems and the trial showed non-inferiority of PP3M over PP1M, for the purposes of this post hoc analysis, PP1M and PP3M data were pooled. Assessments were performed by duration-of-illness groups, categorized as ≤5 years, 6-10 years and >10 years since diagnosis of schizophrenia. Endpoints included PSP scale and PANSS total scores during the DB phase (DB baseline and DB endpoint) and the proportion of patients who met criteria for symptomatic and functional remission at any time during the OL or DB phases that was maintained for ≥3, ≥6, ≥9 or ≥12 months. PANSS remission was defined as individual item scores of ≤3 for PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behaviour), N1 (blunted affect), N4 (social withdrawal), N6 (lack of spontaneity), G5 (mannerisms/posturing) and G9 (unusual thought content) based on the remission criteria defined by the Remission in Schizophrenia Working

Group (Andreasen et al., 2005). The minimum clinically important difference for PANSS is estimated to be 15 points (Hermes, Sokoloff, Stroup, & Rosenheck, 2012). PSP scale functional remission was defined as a total score ≥70. A mean PSP change of ≥7 points is considered clinically meaningful (Nasrallah et al., 2008). Safety and tolerability assessments included evaluation of treatment-emergent adverse events (TEAEs) and clinical laboratory parameters during the OL and DB phases.

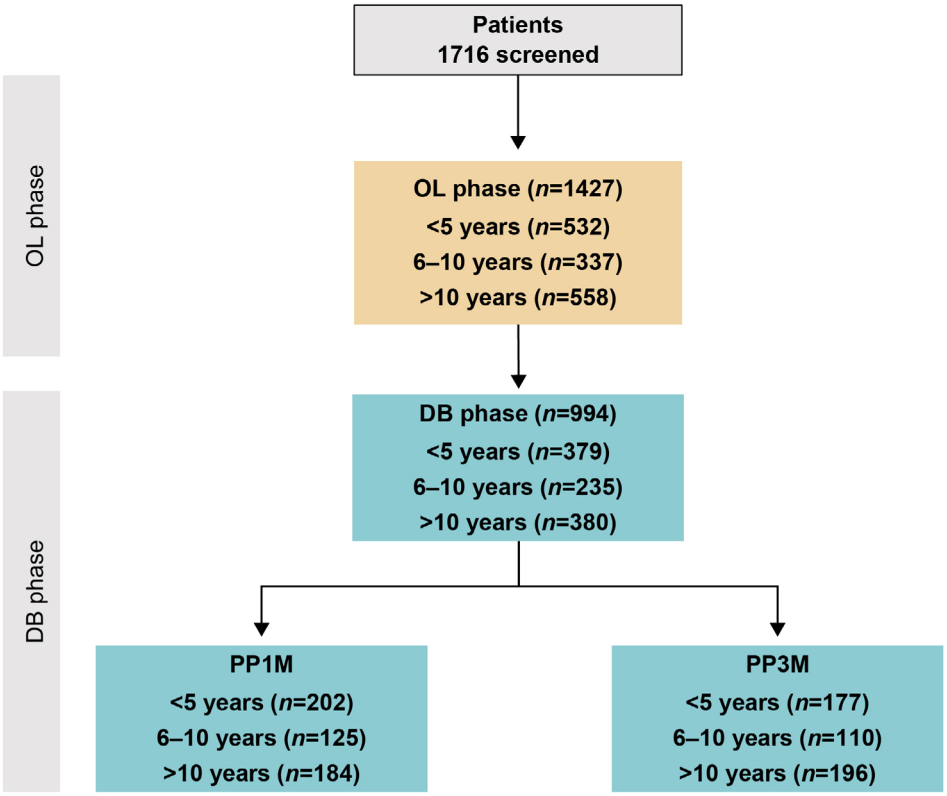
2.4 | Statistical methods/analysis

Demographic and baseline characteristics are summarized descriptively for the DB phase. The modified intent-to-treat analysis set was defined as all randomly assigned patients who received ≥1 dose of study drug during the DB phase. The subpopulation differences were evaluated using analysis of variance (ANOVA) for continuous variables or χ^2 tests for categorical variables. PANSS scores, PSP scale scores and remission status were summarized using descriptive statistics and compared among the groups using ANOVA for continuous variables or χ^2 tests for categorical variables. No adjustments were made for multiplicity. The safety analysis set consisted of all patients who were randomized to the DB phase.

3 | RESULTS

3.1 | Baseline characteristics

A total of 1427 patients were entered in the 17-week OL phase, of which 532 had a duration of illness ≤5 years, 337 had a duration of illness 6-10 years and 558 had a duration of illness >10 years (Figure 1). Of these, 994 patients entered the 48-week DB phase (≤5 years, *n* = 379 [71%]; 6-10 years, *n* = 235 [70%]; and >10 years, *n* = 380 [60%]) and were randomly assigned to PP1M (≤5 years, *n* = 202;



Parameter	≤5 years	6-10 years	>10 years	*P* value
N	379	235	380	
Relapse, *n* (%)				
Yes	29 (8)	17 (7)	39 (10)	
No	350 (92)	218 (93)	341 (90)	
Log rank test				
Overall *P* value				0.304
P value (vs ≤5 y)	—	0.817	0.212	
P value (vs 6–10 y)	—	—	0.193	

FIGURE 1 Patient disposition. DB, double-blind; OL, open-label; PP1M, once-monthly paliperidone palmitate; PP3M, once-every-3-months paliperidone palmitate

TABLE 1 Disposition and demographics of patients who entered the DB phase categorized by duration of illness

	Duration of Illness		
Parameter	**≤5 years**	**6-10 years**	**>10 years**
Patients assessed, *n*	379	235	380
DB phase disposition, *n* (%)			
Completers	280 (73.9)	181 (77.0)	278 (73.2)
Withdrawn or relapsed	99 (26.1)	54 (23.0)	102 (26.8)
P value (vs ≤5 y)		0.382	0.822
P value (vs 6-10 y)			0.285
Age, y			
Mean (SD)	31.5 (10.0)	36.3 (9.6)	47.4 (9.7)
Median (range)	29.0 (18.0-61.0)	35.0 (20.0-68.0)	48.0 (27.0-70.0)
P value (vs ≤5 y)	—	<0.001	<0.001
P value (vs 6-10 y)	—	—	<0.001
Distribution, *n* (%)			
18-25	132 (34.8)	23 (9.8)	0
26-50	226 (59.6)	192 (81.7)	223 (58.7)
51-65	21 (5.5)	18 (7.7)	151 (39.7)
>65	0	2 (0.9)	6 (1.6)
P value (vs ≤5 y)	—	<0.001	<0.001
P value (vs 6-10 y)	—	—	<0.001
Sex, *n* (%)			
Male	191 (50.4)	126 (53.6)	211 (55.5)
Female	188 (49.6)	109 (46.4)	169 (44.5)
P value (vs ≤5 y)	—	0.438	0.157
P value (vs 6-10 y)	—	—	0.644
Race, *n* (%)			
White	187 (49.3)	139 (59.2)	250 (65.8)
Black or African American	16 (4.2)	12 (5.1)	33 (8.7)
Other	176 (46.4)	84 (35.7)	97 (25.5)
P value (vs ≤5 y)	—	0.033	<0.001
P value (vs 6-10 y)	—	—	0.013
BMI, mean (SD), kg/m^2	25.3 (4.8)	26.9 (4.8)	27.5 (5.2)
Region, *n* (%)			
European Union	78 (20.6)	64 (27.2)	142 (37.4)
United States	21 (5.5)	19 (8.1)	40 (10.5)
Non–European Union/Non-United States	280 (73.9)	152 (64.7)	198 (52.1)
Country, *n* (%)[a]			
Argentina	7 (1.9)	7 (3.0)	16 (4.2)
Australia	2 (0.5)	2 (0.9)	1 (0.3)
Austria	0 (0.0)	0 (0.0)	1 (0.3)
Belgium	4 (1.1)	1 (0.4)	6 (1.6)
Brazil	2 (0.5)	7 (3.0)	16 (4.2)
Bulgaria	6 (1.6)	2 (0.9)	20 (5.3)
Canada	4 (1.1)	1 (0.4)	3 (0.8)
China	124 (32.7)	51 (21.7)	34 (9.0)
Czech Republic	19 (5.0)	15 (6.4)	26 (6.8)

(Continues)

TABLE 1 (Continued)

Parameter	Duration of Illness		
	≤5 years	6-10 years	>10 years
France	1 (0.3)	0 (0.0)	2 (0.5)
Germany	4 (1.1)	5 (2.1)	3 (0.8)
Greece	0 (0.0)	2 (0.9)	9 (2.4)
Hungary	15 (4.0)	13 (5.5)	12 (3.2)
Japan	36 (9.5)	19 (8.1)	53 (14.0)
Mexico	2 (0.5)	4 (1.7)	10 (2.6)
Poland	8 (2.1)	7 (3.0)	22 (5.8)
Portugal	2 (0.5)	6 (2.6)	13 (3.4)
Romania	1 (0.3)	3 (1.3)	9 (2.4)
Russian Federation	67 (17.7)	36 (15.3)	42 (11.1)
Slovakia	8 (2.1)	5 (2.1)	9 (2.4)
South Korea	4 (1.1)	7 (3.0)	1 (0.3)
Spain	10 (2.6)	5 (2.1)	10 (2.6)
Taiwan	6 (1.6)	2 (0.9)	6 (1.6)
Ukraine	26 (6.9)	16 (6.8)	16 (4.2)
United States	21 (5.5)	19 (8.1)	40 (10.5)
Age at first diagnosis of schizophrenia, y			
Mean (SD)	28.8 (10.1)	28.7 (9.6)	26.7 (8.1)
Median (range)	26 (14.0-58.0)	27.0 (14.0-61.0)	25.5 (5.0-51.0)
P value (vs ≤5 y)	—	0.889	0.002
P value (vs 6-10 y)	—	—	0.009
Number of hospitalizations for psychosis in 24 months prior to study start, *n* (%)			
Patients assessed, *n*	276	187	324
None	85 (30.8)	76 (40.6)	165 (50.9)
1 time	116 (42.0)	72 (38.5)	103 (31.8)
2 times	60 (21.7)	28 (15.0)	40 (12.4)
3 times	11 (4.0)	6 (3.2)	9 (2.8)
≥4 times	4 (1.5)	5 (2.7)	7 (2.2)
P value (vs ≤5 y)	—	0.127	<0.001
P value (vs 6-10 y)	—	—	0.283

Abbreviations: —, not applicable; BMI, body mass index; DB, double-blind; SD, standard deviation.
[a]Two patients from Sweden did not enter the DB phase and were not included.

6-10 years, *n* = 125; and > 10 years, *n* = 184) or PP3M (≤5 years, *n* = 177; 6-10 years, *n* = 110; and > 10 years, *n* = 196).

There were no significant differences in the proportion of patients who met OL stabilization criteria and entered the DB phase among the duration-of-illness groups (all comparisons, *P* > .05). Similarly, there were no significant differences in the proportion of patients who completed the DB phase among the duration-of-illness groups (all comparisons, *P* > .05; Table 1). Patients in the ≤5-year group were significantly younger than those in the 6-10-year and > 10-year groups (*P* < .001 for all comparisons). Most study participants resided outside of Europe and the United States, with China, the Russian Federation and Japan being the most common countries of origin (Table 1). There was a greater proportion of patients from China and the Russian Federation in the ≤5-year group than in the 6-10- and >10-year groups. Most patients were white, with significantly more white patients in the >10-year vs the ≤5-year group. Patients in the ≤5-year group had significantly more hospitalizations for psychosis in the previous 2 years than those in the >10-year group (Table 1). No significant differences existed in the incidence of relapse or all-cause discontinuation between the ≤5-year, 6-10-year and >10-year groups.

3.2 | PANSS and PSP Scale Scores

Mean PANSS scores were similar among the duration-of-illness groups at OL baseline (range, 84.7-85.6; Figure 2). At the end of the

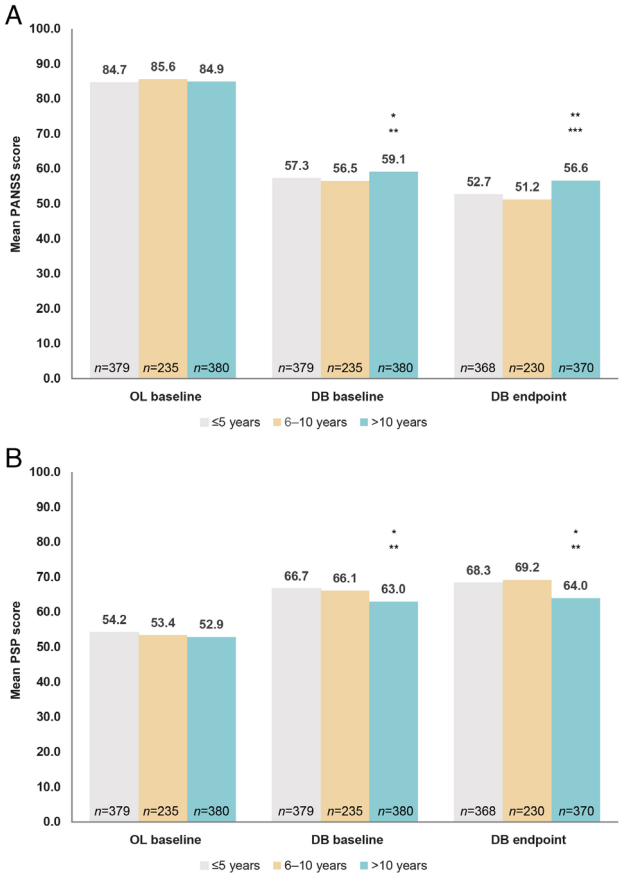


FIGURE 2 PANSS (A) and PSP scale (B) scores' improvement from baseline (by duration of illness). Panel A: **P* = .003 vs ≤5-year; ***P* < .001 vs 6-10-year; ****P* < .001 vs ≤5-year. Panel B: **P* < .001 vs ≤5-year; ***P* < .001 vs 6-10-year. DB, double-blind; OL, open-label; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; SD, standard deviation

OL phase (DB baseline), PANSS scores decreased significantly in all duration-of-illness groups, with mean changes from OL baseline ranging from −25.8 to −29.1 (all groups, *P* < .001). Improvements in total PANSS scores continued through the DB phase, with mean changes from DB baseline to DB endpoint ranging from −2.5 to −5.2 (all groups, *P* < .001; Figure 2). At DB endpoint, mean PANSS scores were significantly lower in the ≤5-year and 6-10-year groups compared with the >10-year group (both comparisons, *P* < .001), suggesting greater symptomatic improvement within these groups.

A similar trend was observed with total PSP scale scores. No significant differences were observed in PSP scale scores at OL baseline (range, 52.9-54.2; Figure 2). At the end of the OL phase (DB baseline), PSP scale scores increased significantly in all duration-of-illness groups, with mean changes from OL baseline ranging from 10.1 to 12.6 (all groups, *P* < .001). Improvements in total PSP scale scores continued through the DB phase. Mean changes in PSP scale scores from DB baseline to DB endpoint ranged 0.8-3.1, with significant differences observed in the ≤5-year and 6-10-year groups (*P* = .002 and *P* < .001, respectively; Figure 2). At DB endpoint, mean PSP scale scores were significantly higher in the ≤5-year and 6-10-year groups vs the >10-year group (both comparisons, *P* < .001), suggesting greater functional improvement within these groups.

3.3 | PANSS and PSP Symptom Remission

A meaningful proportion of patients in all duration-of-illness groups met and maintained PANSS remission criteria at any point during the OL or DB phase (maximum duration ~16 months): 68%-73% maintaining remission for 3 months, and 33%-49% maintaining remission for 12 months. However, the shorter-duration-of-illness groups (ie, ≤5-year and 6-10-year groups) had a higher proportion of patients who met the criteria for PANSS remission lasting for ≥3, ≥6, ≥9 and ≥12 months vs those in the longer-duration-of-illness group (ie, >10 years; Figure 3). Compared with the >10-year group, these differences were statistically significant for the 6-10-year group for ≥9 months and for the ≤5-year and 6-10-year groups for ≥12 months (all comparisons, *P* < .05).

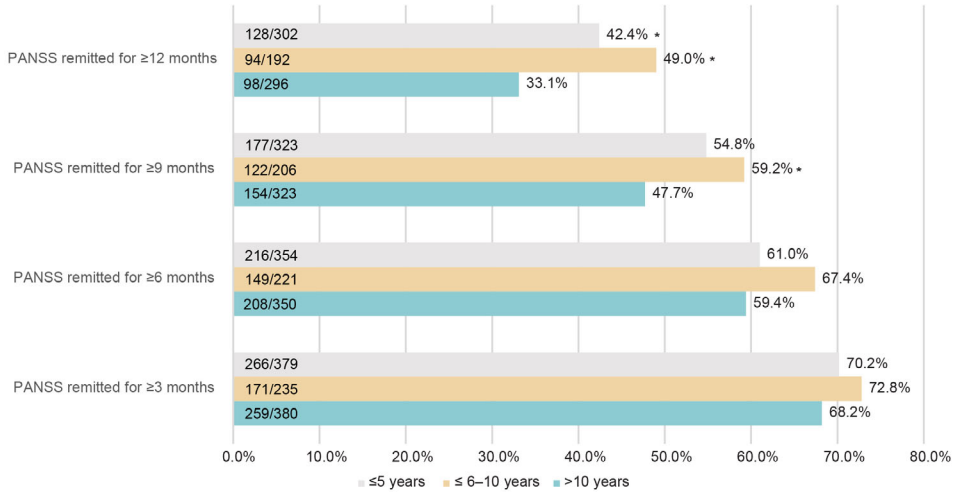
Analysis of PSP scale findings showed a trend similar to, but even more pronounced than, that of the PANSS findings. A meaningful proportion of patients in all duration-of-illness groups met and maintained PSP scale remission criteria at any point during the OL or DB phase, with 36%-46% maintaining remission for 3 months and 16%-27% maintaining remission for 12 months. Yet the shorter-duration-of-illness groups (ie, ≤5-year and 6-10-year groups) had a higher proportion of patients who met the criteria for PSP remission lasting for ≥3, ≥6, ≥9 and ≥ 12 months vs those in the longer-duration-of-illness group (ie, >10 years; Figure 4). Compared with the >10-year group, these differences were statistically significant at all time points for both the ≤5-year and 6-10-year groups (all comparisons, *P* < .05).

3.4 | Dosing by duration of illness

Approximately 86%-90% of patients in each duration-of-illness group received final maintenance doses of PP1M at week 13 of 156-234 mg, of which the equivalent dose became the fixed dose for the remainder of the trial. Slightly more patients in the ≤5-year duration-of-illness group received the lower doses of PP1M (78-117 mg) than those in the 6-10- and >10-year groups (14.5% vs 11.9% and 11.3%, respectively), but this small difference was not considered meaningful.

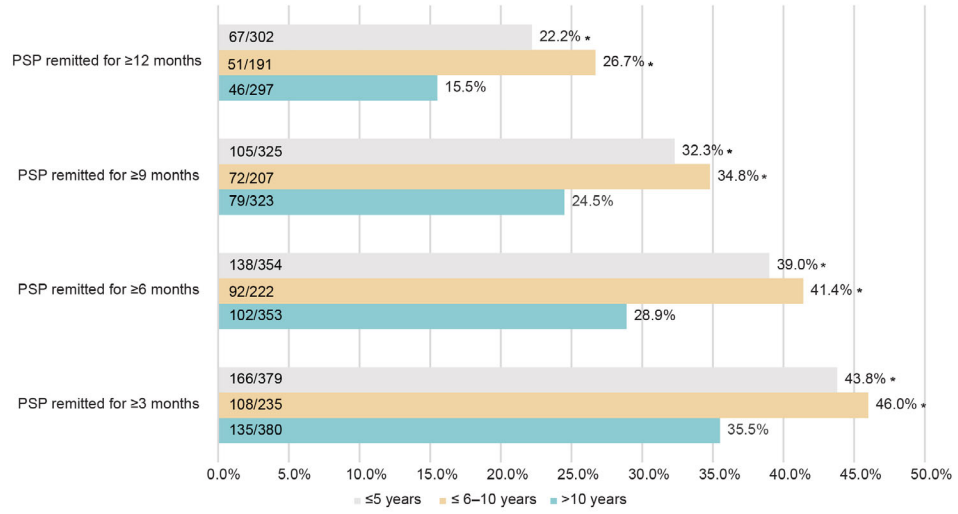
3.5 | Safety

TEAEs were reported in similar proportions of patients among the duration-of-illness groups in the OL and DB phases (Table 2). The incidence of patients reporting any TEAE was similar between the duration-of-illness groups and spanned 50.0%-54.9% in the OL phase and 64.2%-70.2% in the DB phase. Injection site pain and increased weight were the most commonly reported TEAEs in the OL and DB phases, respectively. In the DB phase, two TEAEs had a magnitude of difference between treatment groups of >5%: increased weight, which occurred more commonly in the ≤5-year duration-of-illness group (28.8%) than in the 6-10- and >10-year groups (19.2% and



* *P*<0.05 vs >10-year group

FIGURE 3 Proportion of patients who met PANSS remission criteria† at any time and maintained remission for at least 3, 6, 9 and 12 months during OL and DB phases. *$P < .05$ vs 10-year group. DB, double-blind; OL, open-label; PANSS, Positive and Negative Syndrome Scale. †Defined as individual item scores of ≤3 for PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behaviour), N1 (blunted affect) N4 (social withdrawal), N6 (lack of spontaneity), G5 (mannerisms/posturing) and G9 (unusual thought content) (Andreasen et al., 2005)



* *P*<0.05 vs >10-year group

FIGURE 4 Proportion of patients who met PSP scale remission criteria† at any time and maintained remission for at least 3, 6, 9 and 12 months during OL and DB phases. *$P < .05$ vs 10-year group. DB, double-blind; OL, open-label; PSP, Personal and Social Performance. †Defined as a total PSP scale score ≥70

14.7%, respectively), and nasopharyngitis, which occurred more commonly in the >10-year duration-of-illness group (9.5%) than in the ≤5- and 6-10-year groups (4.0% and 7.2%, respectively). Prolactin-related adverse events (AEs) were higher in the <5- and 6-10-year groups than in the >10-year group in OL and DB phases.

Mean fasting glucose, cholesterol (total, high-density lipoprotein and low-density lipoprotein) and triglyceride values were generally normal for all duration-of-illness groups in the OL and DB phases (Table 2).

4 | DISCUSSION

This post hoc analysis of PP1M and PP3M efficacy on symptom severity and functional remission in patients with schizophrenia with differing durations of illness provides evidence to support the use of LAIs during all phases of schizophrenia, including early-stage illness. Although improvement in symptom severity and functional outcomes was observed across all duration-of-illness groups, patients with shorter (≤5- and 6-10-year) duration of illness had better responses than those with longer (>10-year) duration of illness. Further, symptom stabilization and both symptomatic and functional remission were obtained by more patients with shorter durations of illness and were maintained for longer periods of time. The reasons underlying these differences in the duration of illness groups is unknown but may be due to poorer treatment response in patients with longer duration of illness owing to development of treatment resistance.

These findings support the premise that LAIs are effective in patients with schizophrenia, regardless of duration of illness; however, the magnitude of the response appeared to be even greater in those with ≤5- and 6-10-year durations of illness. Historically, LAIs have been reserved for patients who demonstrate repeated non-adherence to pharmacological treatment, and many psychiatrists avoid

TABLE 2 Treatment-emergent adverse events occurring at an incidence of ≥5% in any group in either phase and change from baseline to endpoint in laboratory parameters

	OL Phase			DB Phase		
	≤5 years*n* = 379	6-10 years*n* = 235	>10 years*n* = 380	≤5 years*n* = 379	6-10 years*n* = 235	>10 years*n* = 380
AEs, *n* (%)						
Any AE	208 (54.9)	129 (54.9)	190 (50.0)	266 (70.2)	157 (66.8)	244 (64.2)
Injection site pain	34 (9.0)	27 (11.5)	30 (7.9)	7 (1.9)	9 (3.8)	10 (2.6)
Weight increased	18 (4.8)	17 (7.2)	8 (2.1)	109 (28.8)	45 (19.2)	56 (14.7)
Akathisia	24 (6.3)	10 (4.3)	9 (2.4)	17 (4.5)	10 (4.3)	6 (1.6)
Anxiety	24 (6.3)	15 (6.4)	11 (3.0)	16 (4.2)	16 (6.8)	16 (4.2)
Insomnia	20 (5.3)	14 (6.0)	15 (4.0)	13 (3.4)	12 (5.1)	14 (3.7)
Nasopharyngitis	13 (3.4)	11 (4.7)	23 (6.1)	15 (4.0)	17 (7.2)	36 (9.5)
Headache	8 (2.1)	8 (3.4)	12 (3.2)	11 (2.9)	11 (4.7)	22 (5.8)
Prolactin-related AEs, *n* (%)						
Any AE	18 (4.8)	14 (6.0)	11 (2.9)	26 (6.9)	13 (5.5)	7 (1.8)
Amenorrhoea	5 (1.3)	3 (1.3)	5 (1.3)	4 (1.1)	6 (2.6)	2 (0.5)
Galactorrhoea	7 (1.9)	4 (1.7)	1 (0.3)	7 (1.9)	0 (0)	1 (0.3)
Irregular menstruation	6 (1.6)	1 (0.4)	0 (0)	7 (1.9)	2 (0.9)	0 (0)
Menstrual disorder	3 (0.8)	1 (0.4)	0 (0)	6 (1.6)	0 (0)	0 (0)
Delayed menstruation	2 (0.5)	1 (0.4)	1 (0.3)	6 (1.6)	1 (0.3)	1 (0.3)
Hypomenorrhoea	0 (0)	3 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)
Retrograde ejaculation	0 (0)	0 (0)	2 (0.5)	0 (0)	0 (0)	0 (0)
Breast discharge	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.9)	0 (0)
Breast pain	0 (0)	1 (0.4)	0 (0)	0 (0)	1 (0.4)	1 (0.3)
Dysmenorrhoea	0 (0)	0 (0)	0 (0)	2 (0.5)	0 (0)	0 (0)
Erectile dysfunction	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.4)
Breast disorder	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
Gynecomastia	0 (0)	0 (0)	1 (0.3)	1 (0.3)	0 (0)	0 (0)
Lactation disorder	0 (0)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)
Metrorrhagia	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)
Vulvovaginal pruritus	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)
Sexual dysfunction	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)
Change from baseline to endpoint in laboratory parameters, mmol/L						
Fasting glucose						
n	368	228	366	359	221	349
Mean baseline (SD)	5.4 (1.16)	5.4 (1.00)	5.6 (1.05)	5.4 (1.13)	5.6 (1.35)	5.7 (1.32)
Mean change (SD)	0.04 (0.86)	0.14 (1.26)	0.24 (1.12)	0.15 (0.89)	0.02 (0.79)	−0.06 (1.17)
Fasting cholesterol						
n	367	228	364	358	221	347
Mean baseline (SD)	4.7 (1.14)	4.8 (1.04)	5.1 (1.07)	4.8 (1.10)	5.0 (1.07)	5.1 (1.04)
Mean change (SD)	0.12 (0.79)	0.17 (0.81)	−0.02 (0.80)	0.05 (0.76)	−0.02 (0.73)	0.06 (0.71)
Fasting HDL cholesterol						
n	367	228	364	358	221	347

(Continues)

TABLE 2 (Continued)

	OL Phase			DB Phase		
	≤5 years*n* = 379	6-10 years*n* = 235	>10 years*n* = 380	≤5 years*n* = 379	6-10 years*n* = 235	>10 years*n* = 380
Mean baseline (SD)	1.4 (0.35)	1.3 (0.42)	1.4 (0.39)	1.4 (0.37)	1.4 (0.42)	1.4 (0.39)
Mean change (SD)	0.01 (0.26)	0.01 (0.27)	−0.02 (0.26)	−0.04 (0.29)	−0.04 (0.26)	−0.02 (0.26)
Fasting LDL cholesterol						
n	367	228	364	358	221	347
Mean baseline (SD)	2.7 (0.97)	2.8 (0.90)	3.0 (0.92)	2.8 (0.94)	3.0 (0.95)	3.0 (0.90)
Mean change (SD)	0.10 (0.67)	0.16 (0.68)	0.3 (0.68)	0.07 (0.67)	0.04 (0.62)	0.05 (0.63)
Fasting triglycerides						
n	367	228	364	358	221	347
Mean baseline (SD)	1.4 (0.82)	1.6 (1.01)	1.7 (1.03)	1.4 (0.88)	1.6 (1.03)	1.6 (0.84)
Mean change (SD)	0.05 (0.84)	0.01 (1.02)	−0.06 (0.82)	0.08 (0.76)	−0.04 (0.81)	0.05 (0.76)

Abbreviations: AE, adverse event; DB, double-blind; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OL, open-label; SD, standard deviation.

prescribing LAIs to patients with first-episode schizophrenia (Altamura et al., 2012; Jeong & Lee, 2013). Although data regarding LAI use in the treatment of early-stage schizophrenia are sparse, there is consensus among experts that antipsychotic treatment should be initiated as soon as possible after diagnosis to promote optimal outcomes, which is supported by our functional remission findings (Altamura et al., 2012; Buchanan et al., 2010; Heres, Lambert, & Vauth, 2014; Jeong & Lee, 2013; Remington et al., 2017). In fact, the recently issued Canadian Schizophrenia Guidelines recommend that LAIs could be used earlier in the course of treatment and not be limited to when physicians have concerns regarding their patients' non-adherence (Remington et al., 2017). The guidelines also recommend that patients always be given the choice of oral or depot antipsychotics (Remington et al., 2017).

Other published studies support our findings regarding the improvement of symptom severity and functioning following treatment with LAIs. Hargarter et al. conducted a post hoc analysis of a prospective, interventional, single-arm, multicentre, OL, 6-month study to evaluate the treatment response (defined as ≥20% improvement of PANSS total score from baseline to endpoint) of PP1M in patients with non-acute schizophrenia with recent (≤3-year) or chronic (>3-year) illness (Hargarter et al., 2016). A ≥20% improvement of PANSS total score was observed in 71.4% of recently diagnosed patients and 59.2% of chronic patients (Hargarter et al., 2016). Moreover, 39.4% of recently diagnosed patients and 24.6% of chronic patients achieved ≥50% improvement in PANSS total score (Hargarter et al., 2016). Post hoc analyses of patients with recently diagnosed (≤3-year) schizophrenia who were treated with risperidone LAI demonstrated significant improvements in total PANSS scores with continued improvements for up to 6 months (Parellada et al., 2005). Approximately 40%, 10%, 9% and 5% of patients had a PANSS score that improved from baseline by ≤20%, ≤30%, ≤40% and ≤50%, respectively (Parellada et al., 2005). Additionally, Kim et al. demonstrated that recently diagnosed patients in a naturalistic setting who received LAIs had significant improvements in PANSS scores over 12 months (Kim et al., 2008).

The present analysis found no new significant safety issues with the use of paliperidone palmitate. The safety and tolerability profile observed in this post hoc analysis was consistent with that of the original study findings (Savitz et al., 2016). Proportions of TEAEs were relatively similar between the duration-of-illness groups in the OL and DB phases, and glucose and lipid profiles were generally within their normal ranges. Other studies have reported that patients with first-episode schizophrenia are more likely to experience TEAEs compared with patients with multi-episode schizophrenia (Buchanan et al., 2010). In this analysis, the overall rates of TEAEs were very similar across the different duration-of-illness groups. The largest difference existed in the reported rates of increased weight, occurring at incidences of 29%, 19% and 15% in the ≤5, 6-10 and >10-year groups, respectively, during the DB phase. This finding is not unexpected because weight gain is a well-recognized AE associated with most antipsychotics, with the risk of weight gain appearing to be highest during the first year of treatment (Dayabandara et al., 2017). Also, the percent of prolactin-related AEs was higher in the <5- and 6-10-year groups than the >10-year groups. A prior analysis had found that serum prolactin decreases with age (Vekemans & Robyn, 1975) and since patients in the current analysis with earlier illness were younger than those in the >10-year group, the difference in AE rates might be due to the increased surge that results from exposure to a D2 antagonist in a young person. In the present analysis, baseline body mass index values differed significantly (25.3, 26.9 and 27.5 kg/m^2 in the ≤5, 6-10 and >10-year groups, respectively; $P < .001$), suggesting that patients later in the illness have likely already experienced antipsychotic-related weight gain.

The present post hoc analysis has several limitations that should be considered when interpreting the results. First, the original trial was a non-inferiority study and was not designed to evaluate or compare the effect between PP1M and PP3M on symptom severity and functioning in patients with schizophrenia with differing durations of

illness. Second, patients in early-stage disease experienced significantly more hospitalizations for psychosis in the 2 years before trial enrolment ($P < .0001$) than those with a longer duration of illness. This may indicate that patients in the ≤5-year duration-of-illness group had greater disease severity than those in the longer-duration-of-illness groups. Third, the effect of PP1M and PP3M on symptom severity and functioning may have been confounded by illness chronicity, as patients with a longer duration of illness typically have poorer response to treatment than those with a shorter duration of illness. Finally, regional differences were observed among the duration-of-illness groups, with some groups having a greater proportion of patients from specific countries than others. It is unknown whether this skew in country of origin affected the analysis.

Results of this post hoc analysis show that symptomatic improvements and delayed functional deterioration were observed with PP1M or PP3M treatment in patients with differing durations of schizophrenia. However, the magnitude of the effects was greater in those with early illness than in those with chronic illness. These findings support administration of PP1M and PP3M in the early stages of schizophrenia to improve symptoms and delay functional deterioration. Future studies assessing long-term efficacy and safety of LAIs in early-stage schizophrenia are warranted. These findings also highlight the need for further research to specifically address the efficacy, safety and cost-effectiveness of LAI use in early-phase schizophrenia.

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CONFLICT OF INTEREST

Brianne Brown is an employee of Janssen Scientific Affairs, LLC, and a Johnson & Johnson stockholder. Ibrahim Turkoz is an employee of Janssen Research and Development, LLC, and a Johnson & Johnson stockholder. Branislav Mancevski is an employee of Janssen Scientific Affairs, LLC. Maju Mathews is an employee of Janssen Scientific Affairs, LLC, and a Johnson & Johnson stockholder.

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